HHS Public Access

Author manuscript

Pediatr Crit Care Med. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Pediatr Crit Care Med. 2019 June ; 20(6): 510–517. doi:10.1097/PCC.0000000000001897.

Cardiac Arrest Outcomes in Children with Pre-existing Neurobehavioral Impairment

James R. Christensen, MD,
Department of Pediatric Rehabilitation Medicine, Kennedy Krieger Institute, and Departments of Physical Medicine and Rehabilitation, and Pediatrics, Johns Hopkins University, Baltimore, Maryland

Beth S. Slomine, PhD,
Department of Neuropsychology, Kennedy Krieger Institute, and Departments of Psychiatry and Behavioral Sciences and Physical Medicine and Rehabilitation, John Hopkins University, Baltimore, Maryland

Faye S. Silverstein, MD,
Departments of Pediatrics and Neurology, University of Michigan, Ann Arbor, Michigan

Kent Page, MStat,
Department of Pediatrics, University of Utah, Salt Lake City, Utah

Richard Holubkov, PhD,
Department of Pediatrics, University of Utah, Salt Lake City, Utah

J. Michael Dean, MD, MBA, FCCM, and
Department of Pediatrics, University of Utah, Salt Lake City, Utah

Frank W. Moler, MD, MS, FCCM
Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

Abstract

Objective: To describe survival, and 3-month and 12-month neurobehavioral outcomes in children with pre-existing neurobehavioral impairment enrolled in one of two parallel randomized clinical trials of targeted temperature management.

Corresponding Author: James R. Christensen, M.D., Kennedy Krieger Institute, 707 North Broadway, Baltimore, MD 21205, Christensenj@kennedykrieger.org, Phone: 443-848-8703.

Copyright form disclosure: All authors received support for article research from the National Institutes of Health (NIH). Drs. Christensen's, Silverstein's, and Dean's institutions received funding from the National Heart, Lung, and Blood Institute (NHLBI). Drs. Slomine, Silverstein, Holubkov, and Moler's institutions received funding from the NIH. Dr. Silverstein received funding from March of Dimes. Dr. Page received funding from the NIH. Dr. Holubkov received funding from Pfizer (DSMB membership), Medimmune (DSMB membership), Physicians Committee for Responsible Medicine (biostatistical consulting), St. Jude Medical (biostatistical consulting), Armaron Bio (DSMB membership), American Burn Association (DSMB Membership), and DURECT corporation (biostatistical consulting). Dr. Dean's institution also received funding from the National Institute of Child Health and Human Development and HRSA MCHB EMSC Program.

Additional members of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) Trial Investigators are listed in Supplemental Appendix 1 (Supplemental Digital Content 7)

Design: Secondary analysis of Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) In-Hospital and Out-of-Hospital trials data.

Setting: Forty-one Pediatric Intensive Care Units in the United States, Canada and United Kingdom.

Patients: Eighty-four participants [59 In-Hospital-Cardiac Arrest (IH-CA), 25 Out-of-Hospital-Cardiac Arrest (OH-CA)], 49 males, 35 females, mean age 4.6 years (sd 5.36), with pre-CA neurobehavioral impairment [Vineland Adaptive Behavior Scales-Second Edition (VABS-II) composite score <70]. All required chest compressions for ≥2 minutes, were comatose and required mechanical ventilation after return of circulation.

Interventions: Neurobehavioral function was assessed using the VABS-II at baseline (reflecting pre-CA status), and at 3 and 12-months post-CA, followed by on-site cognitive evaluation. VABS-II norms are 100 (mean) ±15 (sd); higher scores indicate better function. Analyses evaluated survival, changes in VABS-II, and cognitive functioning.

Measurements and Main Results: Twenty-eight of 84 (33%) survived to 12 months [IH-CA=19/59 (32%), OH-CA=9/25 (36%)]. IH-CA (but not OH-CA) survival rate was significantly lower compared to the THAPCA group without pre-CA neurobehavioral impairment. Twenty-five survived with decrease in VABS-II ≤15 [IH-CA 18/59 (31%), OH-CA 7/25 (28%)]. At 3-months post-CA, mean VABS-II scores declined significantly (−5, sd 14, p<0.05). At 12-months, VABS-II declined after OH-CA (−10, sd 12, p <0.05), but not IH-CA (0, sd 15); 43% (12/28) had unchanged or improved scores.

Conclusions: This study demonstrates the feasibility, utility and challenge of including this population in clinical neuroprotection trials. In children with pre-existing neurobehavioral impairment, one-third survived to 12 months and their neurobehavioral outcomes varied broadly.

Keywords

Cardiac arrest; Pediatrics; Outcome; Neurobehavioral; Pre-existing impairment

INTRODUCTION

Cardiac arrest (CA) in children often results in death or neurological impairment. A significant proportion of those who sustain a CA have pre-existing neurobehavioral impairment. (1, 2) While inclusion of persons with disabilities in clinical trials has been encouraged to improve generalizability of results, (3) most pediatric CA outcome studies do not describe pre-CA neurobehavioral functioning, (4–10) and when it is reported, a global measure is used to categorize function. (1, 2) Also, studies reporting detailed neurobehavioral outcomes have excluded subjects with known significant pre-existing developmental disabilities. (11–15)

Recently, two parallel multi-center randomized clinical trials [Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital (THAPCA-IH, NCT00880087) and Out-of-Hospital (THAPCA-OH, NCT00878644)] evaluated two targeted temperature management strategies [therapeutic hypothermia (33°C) and therapeutic normothermia (36.8°C)] in children who were comatose after IH-CA or OH-CA. (16, 17) Detailed pre-CA

neurobehavioral functioning was obtained soon after enrollment, based on caregiver report using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II); scores <70 indicated pre-CA neurobehavioral impairment. Favorable primary outcome was defined as one-year survival without significant neurobehavioral impairment (VABS-II ≥70).

Children with pre-existing neurobehavioral impairment were included in both THAPCA-IH and THAPCA-OH trials, but excluded from primary outcomes, since their baseline scores were below the threshold for 12-month favorable outcome. However, they were included in secondary outcome analyses (survival, change in VABS-II). Hypothermia did not confer a significant benefit in either trial on one-year survival with favorable functional outcome, survival alone, or change in VABS-II. (16, 17) Secondary analyses of detailed neurobehavioral outcomes in 12-month survivors focused on those without significant pre-CA neurobehavioral impairment. (13–15) The principal aim of this secondary analysis of THAPCA-IH/OH data is to report survival, detailed neurobehavioral, and cognitive outcomes one-year after CA in children with pre-existing neurobehavioral impairment (pre-CA VABS-II <70). Complementary aims are to explore differences in outcome in those with pre-CA neurobehavioral impairment after In-Hospital vs Out-of-Hospital CA, and those treated with Normothermia vs Hypothermia. Additionally we evaluate whether survival differed between THAPCA participants with and without pre-CA neurobehavioral impairment.

METHODS

Participants

Six-hundred-twenty-four children (THAPCA-IH 329, THAPCA-OH 295), ≥48 hours and <18 years of age, who received ≥2 minutes of chest compressions, required mechanical ventilation and were comatose after CA, were enrolled in 41 pediatric intensive care units in the United States, Canada and United Kingdom; data were collected from 2009 to 2015. The studies were approved by Institutional Review Boards at each site. Major exclusion criteria included inability to be randomized within 6 hours of return of circulation, a Glasgow Coma Scale motor score of 5 or 6 (age-appropriate lateralized response to pain), trauma, progressive degenerative encephalopathy, and decision to withhold aggressive treatment. Full inclusion and exclusion criteria, randomization, and enrollment details were reported. (16, 17)

At enrollment, 85/624 (13.6%) [THAPCA-IH 60/329 (18.2%), THAPCA-OH 25/295 (8.5%)] with pre-CA VABS-II composite scores <70 [or Pediatric Cerebral Performance Category and/or Pediatric Overall Performance Category scores ≥3 in 8 subjects with missing pre-CA VABS-II] were ineligible for the THAPCA primary outcome. One case was excluded after diagnosis of a progressive degenerative encephalopathy. At twelve-month follow-up, vital status was known for all 84 participants; 28 survived (THAPCA-IH 19, THAPCA-OH 9) and pre-CA VABS-II was obtained for all survivors. This report analyzes outcomes in these 84 cases.

Assessment Measures

Family Functioning—Pre-CA family functioning was measured using the General Functioning Scale of the Family Assessment Device; possible scores 0-4; ≥2 indicates abnormal functioning. (18)

Global Functioning Measures—Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC). (19, 20) PCPC measures neurological functioning. POPC measures overall health (including neurological functioning). These clinician-rated scales have been recommended for reporting outcome following pediatric CA. (21)

Neurobehavioral Outcome Measures—Vineland Adaptive Behavior Scales-Second Edition (VABS-II).(22) VABS-II measures functional skills and provides age-corrected standard scores [mean=100, standard deviation (sd)=15] in four domains (communication, daily living, socialization, motor skills) and an overall adaptive behavior composite. Each domain includes subdomains with developmentally sequenced items, starting with skills typically observed in infancy. VABS-II includes a caregiver rating form and a survey interview (using caregiver as informant) that yield comparable scores. (22) Description of developmental skills typical of score ranges at different ages is available. (14)

Wechsler Abbreviated Scale of Intelligence (WASI). (23) WASI measures intellectual or general cognitive functioning (standardized for ages 6-89 years), including Vocabulary subtest and Matrix Reasoning (non-verbal) subtest. Age-corrected standardized scores were calculated for each subtest individually and combined for general intellectual functioning (Full Scale IQ).

Mullen Scales of Early Learning (Mullen). (24) The Mullen, a measure of cognitive functioning designed for infants and young children, has four scales (visual reception, fine motor, receptive language, and expressive language). Normative data are available through age 5-years-8-months. Age-corrected standardized scores are available for each scale and for overall early learning composite.

All standardized scores were transformed to standard scores; we defined scores 85-115 as average, 70-84 below average, 50-69 impaired, and <50 severely impaired. This definition for severely impaired was chosen because the lowest possible Mullen composite score is 49, and the lowest possible VABS-II composite varies by age. For Mullen scales, raw scores below the lowest score on the normative table for age were referred to as lowest possible scores.

Procedures

Informed consent was signed by a caregiver. Within 24 hours of enrollment, and after review of instructions with a site research coordination, a primary caregiver completed the VABS-II caregiver rating form to assess pre-CA functioning. The research coordinators reviewed the VABS-II form for completion and response accuracy, collected demographics, CA characteristics, and rated pre-CA neurological (PCPC) and overall functioning (POPC).

Three and twelve-months post-CA, a trained research assistant at one site (Kennedy-Krieger Institute, Baltimore, MD), unaware of treatment group assignment, conducted a semi-structured telephone interview to assess neurobehavioral function (including VABS-II). Subsequently, when feasible, children participated in on-site cognitive testing. Children ≥6 years who were reported to have no consistent means of functional communication on the 12-month VABS-II did not undergo additional testing and were assigned lowest possible scores for analyses.

Statistical analysis

Survival at 12 months post-CA was compared between those children with and without pre-CA neurobehavioral impairment using Fisher's exact test. Distributions of continuous variables were compared between the THAPCA-IH and THAPCA-OH groups using t-tests and Wilcoxon Rank-Sum tests. Categorical variables were compared between the groups using Fisher's exact test. Change in VABS-II scores was calculated (3-month – baseline score, 12-month – baseline score, 12-month – 3-month score). Signed-Rank tests evaluated differences between two continuous variables (e.g. between baseline and 12-month scores). All analyses were performed using SAS software, version 9.4 (SAS Institute).

RESULTS

Sample Characteristics

Sample characteristics are reported in Supplemental Table 1 (Supplemental Digital Content 1). Average age at randomization was 4-years-7-months; with half <2 years old. Mean pre-CA VABS-II composite score was 57.6. The majority had moderate or severe impairment on the PCPC/POPC. All but one participant had at least one pre-existing medical condition. The most common pre-existing conditions were neurological, cardiac, and lung or airway disease. Details of pre-existing conditions are presented in Supplemental Table 2 (Supplemental Digital Content 2).

In IH-CA (relative to OH-CA), pre-existing cardiac condition was more common, tracheostomies were less common, number of epinephrine doses was higher, duration of chest compressions was less, and ECMO was used exclusively in this group. Etiology of CA differed significantly (cardiac most common etiology for IH-CA, respiratory for OH-CA).

Twenty-eight of 84 (33%) survived to 12-months. Survival between those with IH-CA vs OH-CA was similar [IH-CA 19/59 (32%), OH-CA 9/25 (36%), p=0.80]. Survival with decrease in VABS-II score from baseline ≤15 was also similar [IH-CA 18/59 (31%), OH-CA 7/25 (28%), p=1.00].

In survivors, mean 12-month post-CA VABS-II composite score was 54.4. The percentage of those classified as moderate, severe or coma (PCPC and POPC ≥3) increased. Comparing OH-CA to IH-CA survivors, the OH-CA group was significantly more impaired, based on the VABS-II (p<0.001), PCPC (p=0.01) and POPC (p=0.02) [Supplemental Table 1 (Supplemental Digital Content 1)]. Also, clinically significant new co-morbidities developed post-CA. In 12-month survivors, 7 of 11 tracheostomies and 10 of 20 gastrostomy tubes were not present pre-CA.

Survival between targeted temperature management treatment groups was similar [Hypothermia: 17/44 (38.6%), Normothermia: 11/40 (27.5%), p=0.36]. Survival with decrease in VABS-II score from baseline ≤15 was also similar [Hypothermia 15/44 (34%), Normothermia 10/40 (25%), p=0.47].

There were no significant differences in demographics, pre-CA functioning or CA characteristics (primary etiology of CA, number of epinephrine doses, CPR duration, or randomization treatment) between survivors and non-survivors, nor between treatment groups (Hypothermia or Normothermia) (data not shown).

In the only analyses using the THAPCA group without pre-CA neurobehavioral impairment for comparison (Table 1), IH-CA (but not OH-CA) survival rate was significantly lower (p=0.014) for those with, compared to those without pre-CA neurobehavioral impairment. (Age was not significantly different between these two groups, p=0.14.)

Neurobehavioral Outcomes in Survivors

Table 2 displays mean pre-CA, 3-month and 12-month VABS-II scores (composite, domains and subdomains), and change scores. Scores declined significantly from pre-CA to 3-months for the VABS-II Adaptive Behavior Composite, 2 domains (Daily Living and Motor Functioning), and 5 subdomains [Personal and Domestic (Daily Living), Play and Leisure (Socialization), and Fine and Gross (Motor Functioning)]. VABS-II scores were significantly more impaired at 12-months compared to pre-CA functioning for only one domain (Daily Living), and 3 subdomains [Personal (Daily Living), Fine (Motor Functioning), and Expressive (Communication)]. There were no significant changes from 3 to 12 months.

Given significant differences in sample characteristics between the IH-CA and OH-CA groups, their 12-month neurobehavioral outcomes were explored separately by evaluating change from baseline (Table 3). In the OH-CA group, VABS-II Composite, 2 domains (Daily Living, Motor Functioning), and 6 subdomains [Expressive (Communication), Personal (Daily Living), Interpersonal Relationship, Play and Leisure (Socialization), Gross and Fine (Motor Functioning)] declined significantly. In the IH-CA group, only one domain (Daily Living) and one subdomain [Personal (Daily Living)] declined significantly between pre-CA and 12 months.

Supplemental Figure 1 (Supplemental Digital Content 3) shows the distribution of VABS-II scores. The VABS-II composite (pre-CA to 12-month) was unchanged or improved in 12/28 (43%) (IH-CA 10/19, OH-CA 2/9), declined ≤15 points in 13/28 (46%) (IH-CA 8/19, OH-CA 5/9), or declined >15 points in 3/28 (11%) (IH-CA 1/19, OH-CA 2/9). None of the nine subjects with pre-CA VABS-II scores <55 (>3sd), declined >15 points (range +8 to −14) [Supplemental Figure 2 (Supplemental Digital Content 4)]. Of those who improved, five attained VABS-II scores within the unimpaired range (≥70) at 12-months, including two whose scores increased over 20 points into the average range (VABS-II composites = 88, 89, age at randomization 1.7 and 1.4 years respectively).

Supplemental Figure 3 (Supplemental Digital Content 5) shows the distribution of PCPC scores at 3 and 12 months, compared to the pre-CA PCPC. At 3-months, no one improved.

At 12-months, 2 improved, 8 were unchanged, and 18 declined 1 to 3 categories (−1, n=9; −2, n=8, −3, n=1). Of those who were unchanged, 7/8 were severely impaired (PCPC 4) pre-CA. Of those with pre-CA PCPC=1 to 3, 17/20 (85%) declined at least one category, while in those with pre-CA PCPC=4 (severe impairment), 1/8 declined one category, 7/8 were unchanged.

Four survivors were rated in coma (PCPC=5) at hospital discharge. At 12-months, one remained in coma (PCPC=5), two had severe disability (PCPC=4) and one was classified with moderate disability (PCPC=3).

Cognitive Outcomes—Of the twenty survivors <6 years of age, sixteen (IH-CA 12, OH-CA 4) completed testing; two were not offered evaluations (United Kingdom sites) and two were lost to onsite testing follow-up. Lowest possible scores were received by 12/16 (75%) on the Mullen composite; by 10 or 11/16 on the four Mullen scales (Table 4). Due to this distribution, Developmental Quotients (developmental age/chronologic age X 100) were calculated for Mullen Scale scores, to more fully understand the range of outcomes. Five of 16 (31%) had Developmental Quotients <20 on all 4 scales, reflecting very profound impairment [Supplemental Figure 4 (Supplemental Digital Content 6)].

Of 8 participants ≥6 years old at 12-month follow-up, 7 had no consistent means of functional communication (based on the 12-month VABS-II) and did not undergo cognitive testing. The one who completed testing received the lowest possible score (55) for Full Scale IQ and the two WASI subtests.

DISCUSSION

This study describes outcomes in a unique cohort of children with pre-CA neurobehavioral impairment, who incurred IH-CA or OH-CA, were successfully resuscitated, were initially comatose post-resuscitation, and enrolled in targeted temperature management clinical trials. One-third survived to one-year post-CA; neither targeted temperature management group (Hypothermia vs Normothermia) nor location of CA (IH vs. OH) was associated with survival. IH-CA (but not OH-CA) survival rate was significantly lower compared to the THAPCA group without pre-CA neurobehavioral impairment. In survivors, significant declines in neurobehavioral function (pre-CA to 3-months and pre-CA to 12-months) were noted, without significant change from 3 to 12-months. Declines were more pronounced after OH-CA than IH-CA. Yet, 43% remained unchanged or had measured improvements.

Survival rates after CA in children vary depending on a multiplicity of factors, but are typically higher after IH-CA than OH-CA. (1) However, in this group, IH-CA and OH-CA survival rates were similar, and IH-CA survival was significantly lower than that for the THAPCA group without pre-CA neurobehavioral impairment. The increased medical complexity of this cohort may partially explain the lower survival rate after IH-CA. Many had multi-system disease, including genetic and congenital cardiac disorders commonly associated with developmental disabilities. All but one participant (99%) had pre-existing conditions, compared to 48.5% (OH-CA) and 90.9% (IH-CA) for all THAPCA enrollees. (25, 26) The medical complexity of this group highlights one of the challenges of their

inclusion in clinical trials, as survival and neurobehavioral baseline and outcomes are not only related to CA and its treatment, but also to other medical morbidities.

Our results confirm important differences between those with IH vs OH-CA, even when assessing only children with pre-CA neurobehavioral impairments. Similar to a cohort study of children with IH and OH-CA, (1) pre-CA neurobehavioral impairment was more common in the IH than OH-CA group. Similar to the overall THAPCA population, the most common etiology of OH-CA was respiratory, and cardiac in IH-CA. (25, 26) Also, as in the THAPCA group without pre-CA neurobehavioral impairment, (13, 14) more pronounced functional declines were discerned after OH-CA than IH-CA.

Declines in function in THAPCA survivors with pre-CA neurobehavioral impairment were less than in those without pre-CA impairment. Average 12-month VABS-II Composite mean change was 0 (IH-CA) and −10 (OH-CA) in those with pre-CA impairment, in comparison with mean declines of −12 (IH-CA) and −33 (OH-CA) in THAPCA survivors without pre-CA impairment. (13, 14) In the THAPCA group without pre-CA impairment, all VABS-II scores (composite, domain and subdomain scores) declined significantly, while significant changes were much less frequent in those with pre-CA impairment.

Smaller and fewer significant declines in children with pre-CA neurobehavioral impairment reflect challenges inherent in measurement of their neurobehavioral declines. Specifically, no one with a pre-CA VABS-II score ≥3sd below the mean (VABS-II <55) demonstrated a decline of ≥1sd. Similarly, PCPC scores did not decline in those with pre-CA severe impairment. However, we identified more areas of decline after OH-CA than IH-CA, even though the mean pre-CA VABS-II in survivors was qualitatively lower in the OH-CA group (51 vs 61). Consequently, although low baseline scores may limit detection of functional declines, with increasing injury severity (as with OH-CA), change can be demonstrated. However, decreased sensitivity to change in outcome measures remains a potential obstacle to inclusion of participants with pre-existing neurobehavioral impairment in primary outcomes measuring neurobehavioral function.

The VABS-II evaluates developmental domains and compares change objectively. In this study, greatest pre-CA impairment was noted on motor functioning and the least on socialization. At 12-months, Daily Living and Motor domains showed the largest declines, and Socialization the smallest. In the Communication domain, only the subdomain of Expressive Language showed a significant decline, and only at 12-months. These trends may in part reflect the young age of many cases analyzed. Early identification of impairment is easier in some domains, such as Daily Living and Motor, since there are multiple objective milestones for young children. In contrast, identification of Expressive Language impairment is more evident later in development, when speech blossoms. Consequently, the expressive language impairment that became significant only at 12-months post-CA could be related to the failure of acquisition of new milestones. Similar to this group, the Socialization domain declined the least in THAPCA survivors without pre-CA impairment, probably due to the easily attainable simple interactions (i.e. social smile) that form the base of abilities measured for this domain. Additionally, certain medical conditions affect specific domains. The Personal subdomain of Daily Living is heavily weighted to eating behaviors.

Consequently, those with gastrostomy-tubes usually score in the impaired range. Also, tracheostomies may interfere with speech development. These significant co-morbidities, gastrostomy-tubes and tracheostomies, were common at 12-month follow-up, the majority of which were new post-CA.

At 12-month follow-up, five participants attained scores in the unimpaired range (two were average), bringing into question the accuracy of pre-CA classifications and demonstrating the difficulty in assessing baseline function in the Intensive Care Unit setting in young, medically complex children. Also, coma resolved in three of the four who were comatose at hospital discharge (one scoring in the unimpaired range at 12-months), illustrating the challenge of early neuroprognostication in this population.

Cognitive testing confirmed severe impairment in 12/16 (75%) of those <6 years of age. All those ≥6 years were severely impaired (1 received the lowest possible scores, 7 were not tested due to lack of a functional means of communication). The Developmental Quotients helped to delineate the range of outcomes in this severely impaired group. However, while cognitive testing adds to our understanding of this group's outcome, its inclusion for similar subgroups in future trials may not be warranted, unless measures with a lower floor are used.

Strengths of this study include the prospective design, relatively large sample size compared to existing reports, broad pediatric age range, high follow-up rate, detailed CA characteristics, baseline assessment of function, and outcome measures assessing multiple domains of functioning (by both caregiver-report and on-site objective assessment). This is a unique CA cohort, restricted to those with pre-existing neurobehavioral impairment, a group under-represented in the literature. Given their clinical examinations after return of spontaneous circulation, they were at high risk for incremental acquired disability from hypoxic-ischemic brain injury. These results provide a framework for understanding the range of possible outcomes in this subset of children after CA, and although limited, represent the best data available at this time. However, results cannot be generalized to all pediatric CA survivors, especially those not comatose in the immediate six-hour post-resuscitation period or other trial exclusion.

Limitations include possible inaccuracies in pre-CA assessment given the necessity to assess pre-CA functioning rapidly, during a time of crisis, often at young ages (<2 years). This was a heterogeneous cohort, and with the modest sample size, it was not feasible to evaluate predictors of outcome (age, acute medical variables). It is unknown how pre-existing deficits influenced likelihood of enrollment in the trials (from the perspectives both of treating physicians and of families). Data collection did not include some variables that might influence outcome (e.g. length of coma, seizure burden, neuroimaging, post-discharge medications, rehabilitation services, subsequent illness and procedures).

CONCLUSION

In children with pre-CA neurobehavioral impairment who were comatose after CA, one-third survived. Survival was lower after IH-CA (but not OH-CA), when compared to those without pre-CA neurobehavioral impairment. Significant declines in neurobehavioral

function occurred in 12-month survivors, more so after OH-CA than IH-CA. However, function remained unchanged or improved in 43%. While the magnitude and frequency of change were different for those with, compared to those without pre-CA neurobehavioral impairment, the main results (categorical outcomes, treatment and group effect) were similar. Results show that this group's inclusion in THAPCA was both feasible and informative, when change from pre-CA functioning was used to evaluate outcomes. However, detecting decline in functioning was challenging, supporting the decision to include them in THAPCA's secondary but not primary outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Moler FW, Meert K, Donaldson AE, et al.: In-hospital versus out-of-hospital pediatric cardiac arrest: A multicenter cohort study. Crit Care Med 2009;37:2259–2267 [PubMed: 19455024]
2. Horisberger T, Fischer E, Fanconi S: One-year survival and neurological outcome after pediatric cardiopulmonary resuscitation. Intensive Care Med 2002;28:365–368 [PubMed: 11904669]
3. Williams AS, Moore SM: Universal design of research: Inclusion of persons with disabilities in mainstream biomedical studies. Sci Transl Med 2011;3:82cm12
4. Bhanji F, Topjian AA, Nadkarni VM, et al.: Survival rates following pediatric in-hospital cardiac arrests during nights and weekends. JAMA Pediatr 2017;171:39–45 [PubMed: 27820606]
5. Li G, Tang N, DiScala C, et al.: Cardiopulmonary resuscitation in pediatric trauma patients: Survival and functional outcome. J Trauma 1999;47:1–7 [PubMed: 10421178]
6. Maryniak A, Bielawska A, Walczak F, et al.: Long-term cognitive outcome in teenage survivors of arrhythmic cardiac arrest. Resuscitation 2008;77:46–50 [PubMed: 18207629]
7. Tibballs J, Kinney S: A prospective study of outcome of in-patient paediatric cardiopulmonary arrest. Resuscitation 2006;71:310–318 [PubMed: 17069956]
8. Del Castillo J, Lopez-Herce J, Matamoros M, et al.: Long-term evolution after in-hospital cardiac arrest in children: Prospective multicenter multinational study. Resuscitation 2015;96:126–134 [PubMed: 26296583]
9. Gupta P, Tang X, Gall CM, et al.: Epidemiology and outcomes of in-hospital cardiac arrest in critically ill children across hospitals of varied center volume: A multi-center analysis. Resuscitation 2014;85:1473–1479 [PubMed: 25110249]
10. Kriel RL, Krach LE, Luxenberg MG, et al.: Outcome of severe anoxic/ischemic brain injury in children. Pediatr Neurol 1994;10:207–212 [PubMed: 8060422]
11. Bloom AA, Wright JA, Morris RD, et al.: Additive impact of in-hospital cardiac arrest on the functioning of children with heart disease. Pediatrics 1997;99:390–398 [PubMed: 9041294]
12. Morris RD, Krawiecki NS, Wright JA, et al.: Neuropsychological, academic, and adaptive functioning in children who survive in-hospital cardiac arrest and resuscitation. J Learn Disabil 1993;26:46–51 [PubMed: 8418189]
13. Slomine BS, Silverstein FS, Christensen JR, et al.: Neurobehavioral outcomes in children after out-of-hospital cardiac arrest. Pediatrics 2016;137:10.1542/peds.2015-3412 Epub 2016 Mar 3
14. Slomine BS, Silverstein FS, Christensen JR, et al.: Neurobehavioural outcomes in children after in-hospital cardiac arrest. Resuscitation 2018;124:80–89 [PubMed: 29305927]
15. Slomine BS, Nadkarni VM, Christensen JR, et al.: Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children. Resuscitation 2017; 115:178–184 [PubMed: 28274812]
16. Moler FW, Silverstein FS, Holubkov R, et al.: Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372:1898–1908 [PubMed: 25913022]

17. Moler FW, Silverstein FS, Holubkov R, et al.: Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med 2017;376:318–329 [PubMed: 28118559]
18. Epstein B, Baldwin L, Bishop D: The McMaster family assessment device. Journal of Marital and Family Therapy 1983;9:171–180
19. Fiser DH: Assessing the outcome of pediatric intensive care. J Pediatr 1992;121:68–74 [PubMed: 1625096]
20. Fiser DH, Long N, Roberson PK, et al.: Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. Crit Care Med 2000;28:2616–2620 [PubMed: 10921604]
21. Zaritsky A, Nadkarni V, Hazinski MF, et al.: Recommended guidelines for uniform reporting of pediatric advanced life support: The pediatric utstein style. A statement for healthcare professionals from a task force of the american academy of pediatrics, the american heart association, and the european resuscitation council. Resuscitation 1995;30:95–115 [PubMed: 8560109]
22. Vineland adaptive behavior scales: Survey forms manual. 2nd Edition Sparrow S, Cicchetti D, Balla D, editors. Minneapolis, MN, NCS Pearson, 2005
23. Wechsler D: Wechsler abbreviated scale of intelligence. New York, NY, Psychological Corporation, 1999
24. Mullen E: Mullen scales of early learning. Circle Pine, MN, American Guidance Service, 1995
25. Meert KL, Telford R, Holubkov R, et al.: Pediatric out-of-hospital cardiac arrest characteristics and their association with survival and neurobehavioral outcome. Pediatr Crit Care Med 2016;17:e543–e550 [PubMed: 27679965]
26. Meert K, Telford R, Holubkov R, et al.: Paediatric in-hospital cardiac arrest: Factors associated with survival and neurobehavioural outcome one year later. Resuscitation 2018;124:96–105 [PubMed: 29317348]

Table 1:

Alive at 12 months, Comparing Groups based on Pre-Cardiac Arrest Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite

Trial Group	Pre-CA VABS >= 70	Pre-CA VABS < 70	P-value
IH	135/267 (50.6%)	19/59 (32.2%)	0.014[a]
OH	87/262 (33.2%)	9/25 (36.0%)	0.826[a]
Combined OH/IH	222/529 (42.0%)	28/84 (33.3%)	0.152[a]

Pre-CA = Pre-Cardiac Arrest

[a]Fisher's exact test.

Table 2.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Mean (Standard Deviation) Adaptive Behavior Composite, Domain, and Subdomain Scores in 12-month survivors (In-Hospital and Out-of-Hospital Trials combined).

VABS-II	N[a]	Pre-CA	Month 3	Month 12	Pre-CA to month 3 change	Pre-CA to month 12 change	Month 3 to month 12 change
Adaptive Behavior Composite	28	57 (9)	53 (17)	54 (18)	−5 (14)[c]	−3 (15)	1 (9)
Communication	28	59 (13)	56 (23)	57 (20)	−3 (26)	−1 (20)	1 (14)
Receptive	28	69 (14)	64 (23)	65 (23)	−6 (23)	−4 (23)	1 (11)
Expressive	28	64 (16)	59 (24)	56 (21)	−5 (24)	−8 (19)[c]	−3 (14)
Written	9	58 (11)	56 (13)	58 (16)	−4 (7)	−3 (9)	1 (5)
Daily Living	28	61 (14)	52 (15)	53 (17)	−8 (16)[b]	−8 (16)[b]	0 (9)
Personal	28	61 (17)	51 (14)	53 (17)	−9 (13)[b]	−9 (14)[b]	1 (9)
Domestic	17	69 (17)	68 (22)	70 (19)	−5 (11)[c]	−7 (13)	−3 (9)
Community	17	64 (16)	63 (21)	66 (20)	−5 (14)	−6 (15)	−1 (7)
Socialization	28	63 (13)	61 (21)	65 (20)	−2 (20)	2 (19)	3 (12)
Interpersonal Relationship	28	67 (14)	63 (23)	64 (23)	−5 (20)	−3 (18)	1 (10)
Play and Leisure	28	68 (14)	64 (20)	64 (20)	−4 (10)[c]	−4 (11)	0 (7)
Coping Skills	17	75 (14)	73 (19)	75 (18)	−4 (20)	−6 (22)	−2 (5)
Motor Functioning	27	57 (14)	49 (18)	53 (20)	−7 (12)[b]	−3 (15)	3 (12)
Gross	27	62 (11)	57 (14)	59 (15)	−4 (10)[c]	−3 (13)	2 (12)
Fine	27	68 (17)	59 (21)	60 (23)	−9 (15)[b]	−7 (17)[c]	1 (10)

Pre-CA = Pre-Cardiac Arrest

[a] N with both Pre-CA and month 12 assessment. One subject with the Pre-CA assessment did not complete the month 3 assessment. The n's also vary because of age differences and missing data. Domestic, community, and coping skills subdomains are not administered to children <1 y of age. Written subdomain is not administered to children <3 y of age.

[b] P-value < 0.01

[c] P-value < 0.05

All p-values from the Signed Rank test.

Table 3.

Mean (Standard Deviation) Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Scores at Pre-Cardiac Arrest and 12-month Follow-Up and Mean (Standard Deviation) Change (Pre-Cardiac Arrest VABS <70) by Trial Group

		IH Group (N=19)			OH Group (N=9)		
VABS-II	**N**[a]	**Pre-CA Scores**	**Follow-Up Scores**	**Change**	**Pre-CA Scores**	**Follow-Up Scores**	**Change**
Adaptive Behavior Composite	28	61 (9)	61 (18)	0 (15)	51 (7)	41 (9)	−10 (12)[c]
Communication	28	63 (13)	66 (19)	3 (20)	50 (10)	39 (8)	−11 (16)
Receptive	28	73 (15)	73 (22)	0 (24)	62 (8)	48 (14)	−14 (19)
Expressive	28	70 (13)	66 (18)	−4 (18)	52 (16)	36 (7)	−16 (19)[c]
Written	9	60 (15)	63 (19)	−3 (14)	56 (9)	52 (8)	−4 (4)
Daily Living	28	64 (15)	58 (18)	−7 (18)[c]	52 (7)	42 (10)	−10 (11)[c]
Personal	28	65 (19)	58 (18)	−8 (16)[d]	52 (9)	42 (7)	−11 (8)[d]
Domestic	17	69 (19)	74 (19)	−3 (12)	69 (15)	61 (18)	−14 (13)
Community	17	70 (15)	71 (20)	−6 (18)	56 (15)	56 (19)	−6 (11)
Socialization[b]	28	66 (14)	72 (20)	6 (20)	55 (9)	49 (11)	−7 (13)
Interpersonal Relationship[b]	28	72 (14)	73 (20)	2 (18)	58 (10)	44 (12)	−14 (14)[c]
Play and Leisure	28	72 (14)	70 (20)	−1 (12)	60 (11)	52 (13)	−8 (8)[c]
Coping Skills	17	80 (17)	80 (19)	−5 (27)	69 (7)	63 (11)	−7 (15)
Motor Functioning	27	60 (14)	60 (19)	0 (15)	51 (10)	38 (13)	−11 (11)[d]
Gross	27	64 (12)	64 (16)	−1 (14)	56 (8)	48 (5)	−8 (7)[c]
Fine[b]	27	71 (18)	69 (21)	−2 (16)	61 (15)	41 (12)	−18 (14)[c]

Pre-CA = Pre-Cardiac Arrest

[a] Number with both Pre-CA and 12 month assessment. The n's also vary because of age differences and missing data. Domestic, community, and coping skills subdomains are not administered to children <1 y of age. Written subdomain is not administered to children <3 y of age.

[b] P-value < .05 from a Wilcoxon rank-sum test comparing the 12 month change in scores between trial groups

[c] .01 ≤ P-value < .05 from a Signed Rank test comparing Pre-CA and follow-up scores.

[d] .001 ≤ P-value < .01 from a Signed Rank test comparing Pre-CA and follow-up scores.

Table 4.

Mullen Scales of Early Learning Composite and Scale Scores for Children < 6 years old at Follow-Up. Combined In-Hospital (N=12) and Out-of-Hospital (N=4)

Score Range	Early Learning Composite	Visual Reception[a]	Fine Motor[a]	Receptive Language[a]	Expressive Language[a]
Lowest possible score	12 (75%)	10 (63%)	11 (69%)	10 (63%)	10 (63%)
50 - 69 (well below average)	2 (13%)	4 (25%)	3 (19%)	4 (25%)	2 (13%)
70 - 84 (below average)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	3 (19%)
85 - 115 (average)	2 (13%)	2 (13%)	2 (13%)	1 (6%)	1 (6%)

[a]Scores were transformed to correspond to a scale with mean 100 and standard deviation 15.